Genetics and visual attention: Selective deficits in healthy adult carriers of the ε4 allele of the apolipoprotein *E* gene

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The ε4 allele of the apolipoprotein *E* (APOE) gene is associated with altered brain physiology in healthy adults before old age, but concomitant deficits in cognition on standardized tests of cognitive function have not been consistently demonstrated. We hypothesized that sensitive and specific assessment of basic attentional functions that underlie complex cognition would reveal evidence of impairment in otherwise asymptomatic individuals. We found that as early as middle age, nondemented carriers of the ε4 allele of the APOE gene showed deficits when visual attention was spatially directed by cues in tasks of visual discrimination and visual search, in comparison to those without the ε4 allele (ε2 and ε3 carriers). Two component attentional operations were selectively affected: (*i*) shifting spatial attention following invalid location cues, and (*ii*) adjusting the spatial scale of attention during visual search. These changes occurred only in the presence of the ε4 allele and without decline in other aspects of attention (vigilance), memory, or general cognition. The results show that specific components of visual attention are affected by APOE genotype and that the course of cognitive aging is subject to selective alteration by a genetic trait.

aging | Alzheimer's disease | genetic risk | memory | spatial attention

Several genetic conditions identified in childhood exert selective effects on both cognition and brain morphology, e.g., Turner syndrome and Fragile-X syndrome (1, 2). The apolipoprotein *E* (APOE) gene also alters brain structure (3, 4), although later in life, but its effects on cognition in healthy individuals—examined largely with global neuropsychological measures—have been found only inconsistently to date. We now show that this genetic trait selectively alters the course of cognitive aging in healthy adults by affecting specific component operations of visual attention.

APOE is a plasma protein that is important in cholesterol transport and myelin integrity (5). APOE is found in the brain plaques and neurofibrillary tangles (6) that are characteristic of Alzheimer's disease (AD), but is present in normal brains as well. The APOE gene is inherited as one of three alleles, ε2, ε3, and ε4, with the ε4 allele conferring increased risk of developing AD in older adults in a "gene-dose" manner (7). The ε2 allele has been claimed to confer a protective effect with regard to AD risk (8). Healthy adults possessing the ε4 allele show significant alterations in brain morphology and physiology in middle age. A morphological analysis with MRI revealed smaller hippocampi in ε4 heterozygotes (possessing one ε4 allele) as compared with individuals lacking an ε4 allele, despite performance on standardized neuropsychological tests similar to those lacking an ε4 allele (4). Smaller hippocampal volumes in ε4 homozygotes (possessing two ε4 alleles) were associated with declines in memory performance (9). Positron-emission tomography studies also have shown that middle-aged individuals homozygous for the ε4 allele showed significant hypometabolism in a number of regions of association cortex—prefrontal, anterior cingulate, parietal, and temporal—again despite neuropsychological test performance similar to individuals without an ε4 allele (ref. 3 and see also ref. 10).

A major problem in the study of brain aging has been the difficulty of demonstrating that specific age-related cognitive deficits are linked to selective brain changes. Investigations of age-related brain atrophy have not been entirely successful in relating cognitive decline to specific patterns of regional brain shrinkage in nondemented elderly (11, 12). On the one hand, neuropathological change may occur years before cognitive change is detected with conventional neuropsychological tests. On the basis of a neuropathological analysis of an extensive sample of postmortem adult brains, Braak and colleagues (13) argued that the roots of AD may extend back to the second decade in individuals destined to develop the disease. On the other hand, evidence of functional deficits in nondemented older adults with the APOE ε4 allele has been reported in some studies (14–17) but not in others (3, 4, 18). All of these studies used standard neuropsychological tests to assess relatively global aspects of general cognitive function. Age-related morphological brain change may therefore underlie age-related cognitive decline but standardized neuropsychological tests may be insufficiently sensitive to detect such decline, particularly in middle-aged adults. Alterations in brain morphology and physiology are seen as early as the fifth decade in APOE ε4 carriers (3, 4, 9), clearly indicating that cognitive deficits could potentially be seen in healthy adults in this age range.

We hypothesized that sensitive assessment of specific cognitive operations, rather than global cognitive functioning, would reveal evidence of cognitive decline as a function of APOE genotype. We therefore chose to assay basic attentional functions that underlie complex cognition. Although previous neuropsychological studies have focused on memory, attentional changes can mediate memory (19) and may precede or coincide with memory decline in AD (20). Therefore, we examined the question of cognitive change in APOE ε4 carriers by investigating narrowly defined aspects of visual attention that have been well studied: shifting of visuospatial attention, scaling of visuospatial attention, and sustained attention.

Visuospatial attention has been characterized as a spotlight or gradient of heightened sensory processing at the location of a relevant stimulus (21, 22). This mechanism is proposed to mediate search for objects among distractors (23, 24) and is claimed to be the first level of visual processing in the human brain of which there is conscious awareness (25, 26). An alter-

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Abbreviations: APOE, apolipoprotein E; AD, Alzheimer's disease; RT, reaction time; SOA, stimulus onset asynchrony.

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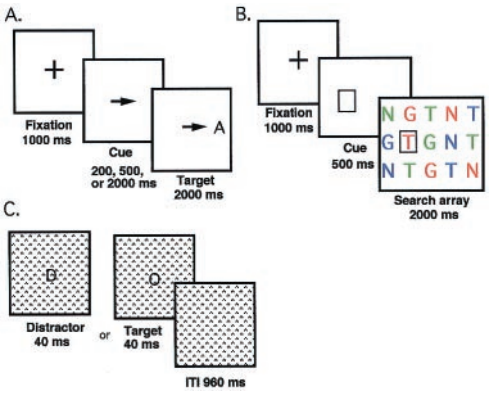

Fig. 1. Representations of three visual attention tasks. (*A*) Cued letter discrimination task. (*B*) Cued visual search task. (*C*) Vigilance task. ITI, intertrial interval.

native conceptualization is that spatial attention is a mechanism for resolving competition for neural processing in inferotemporal cortex between relevant and irrelevant objects (27). Spatial attention also can be fractionated into separate functions of (*i*) shifting spatial attention and (*ii*) adjusting the size or scale of spatial attention (28). A third, also fundamental, form of attention—sustained attention or vigilance—is involved in the maintenance of attention to an infrequently appearing target over a long period (29). We investigated whether the presence of the APOE ε4 allele selectively alters any of these three aspects of attention by assessing performance on a cued discrimination task, a cued visual search task, and a vigilance task in healthy individuals of known APOE genotype.

Study 1

People typically move their head and eyes to a particular location when searching for an object of current interest. This movement allows the object at that location to be accurately perceived because its image falls on the fovea. It is well known, however, that attention also can be allocated *covertly* to a position in the visual field (21). Head and eye movements can be considered the coarse, overt method for choosing a spatial location within which to deploy the more fine-grained mechanism of covert spatial attention. Within a relatively empty field, visuospatial attention can be shifted in response to top-down information about target location. In the Posner covert orienting paradigm (21), such information is provided in the form of arrow or box cues to target location. A valid cue typically reduces reaction time (RT) to the target. When the location cue is not valid (i.e., does not predict target location), attention must be shifted away from the cued location and RT is slowed—this effect is termed attentional disengagement (21, 30). We adapted this paradigm to a cued letter discrimination task (Fig. 1*A*), which we have used in previous studies of both healthy and demented adults (31–33). Manipulation of cue-target stimulus onset asynchrony (SOA) in this task allowed assessment of whether APOE genotype alters the time course of cueing effects on visual discrimination.

Methods. *Participants.* The sample consisted of healthy individuals ($n = 97$) aged 50 years and over who had volunteered to participate in a double-blind longitudinal study. Individuals were excluded from participation if they indicated significant cognitive impairments or fell outside the range of normal on a series of standardized neuropsychological test batteries, including the Mattis Dementia Rating Scale (34), Buschke Selective Reminding Test (35), and the Wechsler Memory Scale (36). Other criteria for exclusion were significant medical problems, including diabetes mellitus, hypertension, cerebrovascular disorder, autoimmune disorder, vitamin B_{12} deficiency, or thyroid disorder. Exclusion of individuals for cerebrovascular disease was made on the basis of history of strokes, hypertension, and review of the MRI scan. Of the 97 individuals tested, 74 had first-degree relatives diagnosed with AD. Demographic characteristics are given in Table 1. Apolipoprotein *E* genotypes were determined by restriction endonuclease digestion of PCR-amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA). All procedures were approved by institutional review and informed consent was obtained from all participants.

The sample size, although relatively large ($n = 97$), was insufficient to group individuals by all possible paired combinations of the three APOE alleles (ε2, ε3, and ε4). Hence, APOE genotypes were combined into the following APOE groups: an "ε2"group (including ε2/ε2 and ε2/ε3), an "ε3" group (including ε3/ε3), and an "ε4"group (including ε2/ε4, ε3/ε4, and ε4/ε4). This grouping was chosen to allow an assessment of the effect of at least one ε4 allele (the ε4 group), while at the same time allowing a comparison of the effect of the ε2 allele independently of the effect of the ε4 allele. The rationale for this grouping was that the ε4 allele is associated with greater risk of developing AD (7), whereas ε2 may provide a protective advantage (8).

The three groups did not differ statistically as to age, gender composition, years of education, or on standardized neuropsychological tests (Table 1). These individuals also are being assessed longitudinally, but at present insufficient data have been collected for analysis of changes over more than 1 year.

Cued letter discrimination task. Following a fixation point (displayed for 500 ms), a centered location cue (an arrow pointing to the left, right, or both directions) appeared. The cue was valid in predicting the subsequent target location on 62.5% of trials, invalid on 18.75%, and neutral on 18.75%. The centered location cue appeared for a variable cue-target SOA (200, 500, or 1,000 ms) after which a letter target appeared 6.7° to the right or left of fixation. Participants were required to make a speeded categorization of the target (consonant or vowel) by pressing one of two response buttons. The intertrial interval was varied (2,200, 2,500, or 2,800 ms).

Results and Discussion. Accuracy on the cued discrimination task ranged from 96.2% to 98.6% and did not differ as a function of APOE group. Median RTs were computed for correct letter discriminations. RT was fastest following valid, slowest following invalid, and intermediate for neutral cues [cue validity, $F(2, 194) = 39.48$, $P < 0.0001$]. Effects of cue validity developed as cue-target SOA increased from 200 to 2,000 ms [SOA, $F(2, 194) = 46.25$, $P < 0.0001$], with RT benefits of valid cues evident

Table 1. Demographic characteristics and mean (±SD) neuropsychological test performance of participant groups

APOE group	*n*	Age, years	Gender (F, M)	Education, years	Mattis dementia scale	Buschke mean score	Buschke delayed score	WMS general score	WMS delayed score
ε2	11	61.8 ± 8.4	7, 4	17.3 ± 1.9	142 ± 1.4	9.7 ± 0.9	9.6 ± 1.7	116.8 ± 16.6	115.5 ± 16.0
ε3	48	59.1 ± 8.5	27, 21	16.6 ± 2.4	141 ± 2.6	9.4 ± 1.3	8.7 ± 2.7	117.4 ± 14.7	115.8 ± 14.31
ε4	38	58.0 ± 1.3	25, 13	16.7 ± 2.2	141 ± 2.3	8.8 ± 1.7	8.6 ± 2.3	114.5 ± 14.2	109.8 ± 15.6

ε2 Group, ε2/ε2 or ε2/ε3; ε3 group, ε3/ε3; ε4 group, ε2/ε4, ε3/ε4, or ε4/ε4. WMS, Wechsler Memory Scale.

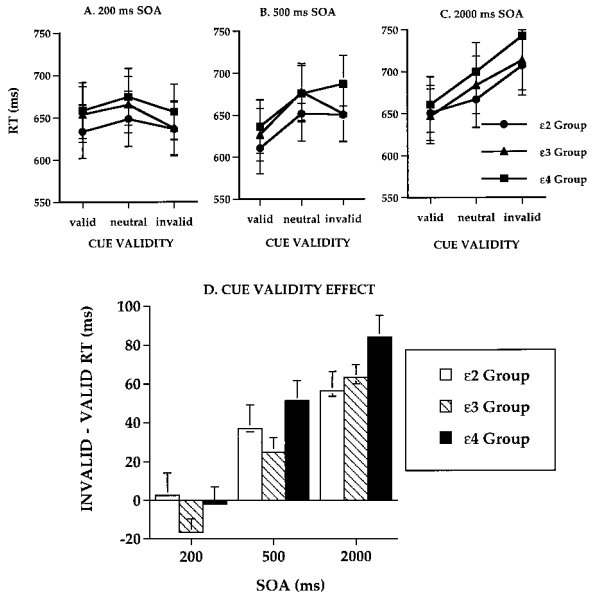

Fig. 2. (*A–C*) RTs in the cued letter discrimination task plotted for the ε2, ε3, and ε4 APOE groups as a function of cue validity and SOA [200 ms (*A*); 500 ms (*B*); 2,000 ms (*C*)]. (*D*) Total cue validity effect (invalid–valid RT) for each APOE group and SOA.

at a shorter SOA than were RT costs of invalid cues (validity × SOA, $F(4, 388) = 18.79$, $P < 0.0001$; Fig. 2).

There was no main effect of APOE group on overall RT. However, the effect of cue validity on RT was greatest in the ε4 group, as evidenced by the group × validity interaction [$F(4, 188) = 2.63$, $P < 0.05$]. As Fig. 2 shows, RT to invalid cues was slowed in the ε4 group as compared with either the ε2 or ε3 groups. This finding was confirmed by analysis of a composite measure of the total cue validity effect (invalid–valid RT), which was largest in the ε4 group [$F(2, 94) = 3.15$, $P < 0.05$] and increased with SOA [$F(2, 188) = 28.52$, $P < 0.0001$] (Fig. 2*D*). Total cue validity effects can be decomposed into costs of invalid cues (invalid–neutral RT) and benefits of valid cues (neutral–valid RT). Costs increased with SOA [$F(2, 188) = 18.17$, $P < 0.0001$] and were greater in the ε4 group than in the ε2 and ε3 groups [$F(2, 98) = 3.56$, $P < 0.03$]. In contrast, the benefits of valid cues varied with SOA [$F(2, 188) = 5.94$, $P < 0.001$] but did not differ between groups.

Study 1 shows that covert shifting of visuospatial attention in response to top-down information about target location is deployed differently in healthy, middle-aged individuals depending on APOE genotype. The difference is selective, with the accuracy of performance, the time course of location cue effects, and the benefit of valid cues all being unaffected by genotype. In contrast, the cost of invalid cues was greater in individuals with at least one ε4 allele as compared with noncarriers with ε2 or ε3 alleles only. The greater effect of cue validity in the ε4 group can be attributed to slowed attentional disengagement (21), as reflected in greater costs of invalid cues, rather than to a change in benefits of valid cues. We previously have shown that individuals in the early, mild stage of AD show a similar, although larger attentional disengagement deficit (31). However, the interpretation of RTs to neutral cues can be problematical because of factors such as differences in arousal. A more conservative interpretation therefore is that the ε4 allele is associated with alteration in the overall efficiency of attentional shifting as reflected in the total cue validity effect. Nevertheless, possession of at least one ε4 allele was associated with a change in attentional processing qualitatively the same as that seen in persons with clinically diagnosed mild AD.

Study 2

The cued letter discrimination task used in Study 1, which signals the location of an isolated object in an otherwise empty visual field, is weakly representative of the way visuospatial attention is typically deployed. In everyday vision, targets are usually embedded in complex visual scenes. The visual search task in which a known object is presented among distractors is a better experimental model of the demands required for such discrimination (37). We cued target location in a visual search task by preceding the search array with a cue varying in size (Fig. 1*B*). We previously have shown that search RT is facilitated by increased precision of the cue in matching the location and size of the target (28, 38–40). The reduction in RT with decreased cue size points to a mechanism for spatial scaling of attention during visual search (28). The cue-size effect is larger in older (>60 years) than in young adults, but then decreases after age 75 years (39) and also is markedly reduced in individuals with AD (38, 40). Use of this task allowed assessment of whether the ability to adjust the spatial scale of attention is altered in healthy persons with the ε4 allele.

Methods. *Cued visual search task.* After a fixation (1,000 ms), a rectangular cue predicted with variable precision the size of the region where a subsequent target appeared in an array of distractors (see Fig. 1*B*). The target was a red **T** presented in a 3 × 5 (6.3 × 4.2°) search array of uppercase letters (**T, N, G**) colored green, red, or blue. The rectangular cue varied in size according to the number of letters enclosed (1, 3, 9, or 15 letters). The inner edge of each array appeared to the left or right of fixation by 3.8°. The cue appeared superimposed over the array until either the subject responded by button press or 2.5 s elapsed. Participants were required to make a speeded decision indicating the presence (83% of trials) or absence (17% of trials) of the target in the letter array by pressing one of two buttons. There were two search conditions: (*i*) easy or feature search, in which the target letter was distinguishable from distractors by a single feature, either red or the letter form **T**, and (*ii*) difficult or conjunction search in which the target properties of color and form appeared with equal frequency among the distractors.

Results and Discussion. All groups performed the cued visual search task accurately. Accuracy ranged from 95.3% to 100% and did not differ between the three APOE groups. Median RTs were computed for correct target responses. RT was faster in the feature than in the conjunction search task [$F(1, 94) = 581.25$, $P < 0.0001$]. RT also slowed as cue size increased [$F(3, 282) = 225.80$, $P < 0.0001$], and this effect was greater in conjunction compared with feature search (task × cue size, $F(3, 282) = 169.13$, $P < 0.0001$). These task effects are similar to those we have reported previously (28, 38–40), thus establishing that the APOE groups performed this task in a similar fashion to unselected healthy adults.

There were no main effects of group on overall RT. Despite the demands on processes of disengagement presumably made by conjunction search, search speed was not significantly slower overall in the ε4 group. However, the effects of cue size on RT varied with APOE group, particularly at the smaller cues (cue size × group, $F(6, 282) = 2.90$, $P < 0.05$) (see Fig. 3*A*). To have a summary measure of the effect of cue size on RT, slopes were calculated by regressing RT on all four cue sizes for each participant. The slope of this RT/cue size function reflects the extent of the postulated attention scaling mechanism: The lower the slope, the lower the effective use of the mechanism (38–40). Analysis of the slopes of the RT/cue size function revealed that slope varied with APOE group [$F(2, 94) = 3.14$, $P < 0.05$], with

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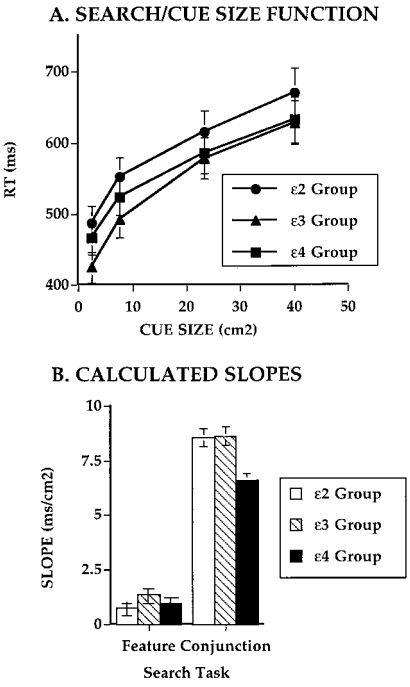

Fig. 3. (*A*) Visual search RTs (averaged over feature and conjunction search) plotted as a function of cue size for the ε2, ε3, and ε4 APOE groups. (*B*) Calculated slope measures of the effects of cue precision for the three groups for the feature and conjunction search tasks.

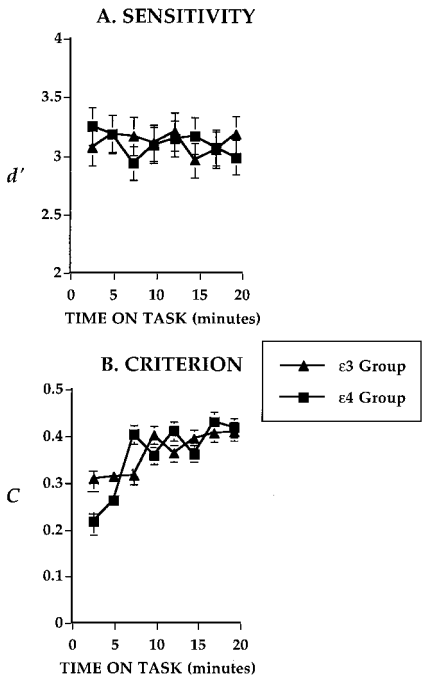

Fig. 4. (*A*) Sensitivity (*d′*) of letter discrimination in the vigilance task for the ε3 and ε4 APOE groups plotted as a function of time on task. (*B*) The response criterion index (*c*) for the three APOE groups plotted as a function of time on task.

the slope being lower in the ε4 group than in the ε2 or ε3 groups (Fig. 3*B*). Thus the spatial scaling of attention was reduced in individuals with the ε4 allele as compared with those without ε4.

These results suggest that possession of at least one APOE ε4 allele is associated with reduced effects on search of top-down information about target size and location. The absence of ε4 is associated with greater effects of such top-down information. In previous work we have shown that healthy adults unscreened for APOE genotype exhibit an increased effect of cue size information up to about 60 years of age, but this effect was reduced in persons aged 75 years and older, with the increase and the decrease occurring evenly over the range of cue sizes (28). In contrast, in the present study the effect of cue size was found to be altered in much younger individuals at increased risk of AD (ε4 group). Furthermore, this effect was seen mainly at the smaller cue sizes, suggesting a selective decline in the ability to constrict spatial attention associated with the presence of the ε4 allele. We have recently reported a similar (but quantitatively greater) deficit in individuals clinically diagnosed with early stage AD (40). Thus, as in the case of the attentional shifting effect in Study 1, possession of at least one ε4 allele was associated with a change in attentional scaling that was qualitatively the same as that seen in persons with clinically diagnosed mild AD.

Study 3

The ability to detect an infrequently appearing target declines over time, a phenomenon known as the vigilance decrement (41). Under demanding conditions with perceptually degraded stimuli, the vigilance decrement can appear within 5 min (42). We used this vigilance task (Fig. 1*C*) to examine whether the attentional changes associated with APOE genotype noted in Studies 1 and 2 were linked to more general changes in arousal and sustained attention.

Methods. *Vigilance task.* This task required discrimination of a target letter (**O**), present on 20% of trials, from distractors (**D** or backwards **D**) against a patterned background. Stimuli were presented once per second for 40 ms in the center of a constantly present masking screen of small circles (Fig. 1*C*). Participants were asked to press a button when they detected a target. Three versions of the task differed in the luminance and contrast of the gray stimuli. Practice began with the hardest version, with easier versions used depending on performance. A total of 920 test trials, lasting about 20 min, were administered continuously. Twenty individuals were unable or unwilling to perform this task in its entirety, reducing the sample size overall. There were no significant differences in any of the demographic variables between this reduced sample and the full sample used in Studies 1 and 2.

Results and Discussion. The percentages of correct target detections and false alarms were computed for each of eight 2.5-min time blocks of the task. These percentages then were used to calculate the signal detection theory measures of sensitivity, d' and response criterion c (43). With time on task, d' declined (Fig. 4*A*) whereas c (Fig. 4*B*) increased [$F(7, 539) = 2.10$, $P < 0.04$]. These changes over time indicate that this task provided valid and sensitive assessment of changes in vigilance (42). However, neither d' nor c differed significantly between the three APOE groups. Because of the small number of individuals in the ε2 group in this task particularly ($n = 6$), only the ε3 and ε4 group data are plotted in Fig. 4. A decrease in d' over time in a similar vigilance task has been reported previously in older adults (44), although the d' values in the present study are higher as compared with those reported from the older individuals (mean age 69.5 years) in the previous study.

We also investigated whether the ε4-related group differences in the cued discrimination and cue search tasks in Studies 1 and 2 were associated with vigilance performance. We computed a vigilance decrement score as the difference in d' between the first and second halves of the 20-min task. This measure was uncorrelated with either the total RT costs and benefits measure

of cued discrimination (at the 2,000-ms SOA) ($r = 0.08$) or the slope measure of cued search ($r = 0.09$).

General Discussion

The results of these studies demonstrate that a genetic trait can selectively affect the course of cognitive aging in healthy, middle-aged adults. The cognitive function affected, visuospatial attention, is a basic aspect of attention that may contribute to the efficiency of functioning of memory and other higher cognitive abilities. Nondemented asymptomatic individuals of mean age less than 60 years who inherited one or two $\varepsilon 4$ alleles of the APOE gene showed specific and selective deficits in visual attention as compared with those possessing the $\varepsilon 2$ or the $\varepsilon 3$ alleles, without the $\varepsilon 4$. These attentional changes occurred without concomitant changes in sustained attention, in memory, or in cognition, broadly defined. Compared to those subjects without an $\varepsilon 4$ allele, $\varepsilon 4$ carriers exhibited deficits in (*i*) shifting spatial attention in response to invalid location cues and (*ii*) adjustment of the spatial scale of attention during visual search. Thus, two specific component operations of attention were affected and the deficits were selective—shifting of attention when cues were valid and scaling of attention when cues were large were unaffected. Moreover, despite these deficits, the ability to perform these relatively simple tasks accurately was retained.

The fact that performance on the vigilance task did not vary with APOE genotype indicates that the changes in visual attention were not caused by more global or nonspecific changes in arousal. The absence of correlations between vigilance performance and measures of shifting and scaling visuospatial attention indicates that the $\varepsilon 4$-related group differences on these measures were not mediated by differences in sustained attention ability. Components of visual attention were therefore selectively affected in individuals with the APOE $\varepsilon 4$ allele. The findings show that decline in specific aspects of cognitive functioning can occur as early as the fifth decade in healthy adults, and provide evidence of a genetic basis for such attentional deficits.

The $\varepsilon 4$ allele has also been established as a risk factor for AD (7). The appearance in the present study of deficits in healthy $\varepsilon 4$ carriers in attentional functions before deficits in memory systems represents an inversion of the order thought to occur in AD, in which memory is believed to decline first and in isolation, followed by declines in attention processes (45). However, this generally accepted sequence may be simply an outcome related to definition, because the clinical diagnosis of AD requires a memory deficit (20, 46). Could attentional rather than memory changes be the first presenting symptom of AD? A firm answer to this question must await further longitudinal examination using sensitive measures of both attention and memory in individuals typed for APOE.

The attentional changes in nondemented $\varepsilon 4$ carriers reported in this study are qualitatively similar (but not quantitatively equivalent) to attentional deficits in persons with clinically diagnosed AD. Specifically, individuals with mild to moderate AD exhibit slowed attentional disengagement in cued discrimination tasks (31) and reduced benefit of cue precision during visual search tasks (38–40). On the other hand, sustained attention is mildly affected, if at all, in the early stages of AD (46), unless the vigilance task incorporates a memory load (47), in which case AD patients are impaired (48). This pattern of selective deficits in the shifting and scaling of spatial attention, with relative sparing of sustained attention in AD, is exactly that found in the present study in nondemented, middle-aged carriers of the $\varepsilon 4$ allele.

These attentional changes are distinct in many respects from those associated with normal adult aging. Slowed attentional disengagement following invalid cues has been shown previously to occur only in older adults over the age of 75 (33), well beyond the mean age of the $\varepsilon 4$ group in this study. We also have previously found that compared with the young, the effect of precue precision on visual search is *increased* in older adults until about age 75 (28). This result is in contrast to the present study where the same effect *decreased* in middle-aged adults with an $\varepsilon 4$ allele. Effects of precue size (precision) decrease after age 75 (28, 39). Moreover, in AD there is a selectively reduced benefit from precise precues. This effect also was exhibited by $\varepsilon 4$ carriers in the present study but is not seen in unselected healthy older adults (39). Thus, the reduction in cue-size effects during visual search in APOE $\varepsilon 4$ carriers is different from the pattern seen in healthy aging before age 75 but is similar to the pattern seen both in unscreened elderly over the age of 75 and in individuals with clinically diagnosed AD. Finally, the vigilance decrement also is unaffected by normal aging, at least until the age of 75 (44). Thus $\varepsilon 4$ carriers show a pattern of deficits in visual attention closer to that seen in diagnosed AD patients than to that associated with normal aging.

In contrast to APOE $\varepsilon 4$, the $\varepsilon 2$ allele has been associated with decreased risk of AD (49), although the effect may vary with ethnic group (50). In nondemented individuals the $\varepsilon 2/\varepsilon 3$ genotype shows less neuropathology compared with the $\varepsilon 3/\varepsilon 3$ genotype (8). In our sample, those subjects possessing an $\varepsilon 2$ but not an $\varepsilon 4$ allele performed similarly to the $\varepsilon 3/\varepsilon 3$ genotype, suggesting a neutral effect of the $\varepsilon 2$ allele on the specific attentional operations assessed in this study. This conclusion is limited by the small sample of individuals in the $\varepsilon 2$ group ($n = 11$).

What is the neural basis for the effect of APOE genotype on visual attention in healthy individuals before old age? Positron-emission tomography studies have shown that metabolism of association cortex is reduced in $\varepsilon 4$ homozygotes (3) similar in mean age to those in the present study. One of the regions shown to be hypometabolic, parietal association cortex, is known to be involved in the mediation of shifts of spatial attention in both covert orienting (51, 52) and visual search tasks (24). Increased costs of invalid cues have been specifically associated with superior parietal lesions (30). The requirement to make large adjustments of attentional scale in the "global/local" task activates temporal-parietal cortex (53). Therefore, both shifting and scaling of visuospatial attention require activation of brain regions whose metabolism has been found to decline from youth to old age in healthy individuals (54) and also in individuals in the early stages of AD (55).

Research on brain cholinergic systems also supports a link between APOE polymorphism and spatial attention. Increased APOE $\varepsilon 4$ gene dose is associated with reduced hippocampal and cortical choline acetlytransferase (ChAT) activity (56). Consistent with that observation, impairments in cognition and in ChAT levels in basal forebrain projections of APOE-deficient (knockout) mice (57) are reversed by cholinergic replacement therapy (58). These results indicate that APOE plays a role in the integrity of the basal forebrain cholinergic system. Pharmacological manipulation of cholinergic neurotransmission has been shown to influence spatial attention in both covert orienting (59, 60) and visual search tasks (61). Furthermore, lesions of the basal forebrain induced by ibotenic acid have been found to affect attentional disengagement in a covert orienting task, without concomitant effects on memory (62). Therefore, reduced efficiency of cholinergic projections to parietal [mediating disengagement of attention (51, 52)] and temporal [mediating scaling of attention (53)] cortices could underlie the impairments in visuospatial attention in the APOE $\varepsilon 4$ group in the present study.

Our results indicate that specific components of visual attention are affected by APOE genotype. Furthermore, the course of cognitive aging is altered in nondemented $\varepsilon 4$ carriers as compared with those with the $\varepsilon 2/\varepsilon 3$ and $\varepsilon 3/\varepsilon 3$ genotypes. As such, the findings verify previous reports, using more general neuropsychological measures, of cognitive decline in APOE $\varepsilon 4$ carriers (14–17). The results also suggest that such cognitive decline may arise in part from reduced efficiency in attentional shifting and scaling of spatial attention. In the present study, $\varepsilon 4$ carriers were found to have

undergone selective and specific cognitive change at a mean age of 58 years. These findings are of interest because of the difficulty in demonstrating age-related decrements in attention and cognition before age 65 (63). The results indicate that selective attentional changes occur several years before the onset of symptoms in individuals at increased risk of developing AD. That these changes are seen in the absence of memory loss or general cognitive decline suggests that attentional processes are selectively altered early in the course of APOE ε4-related brain change, despite evidence of concurrent physiologic decline in several regions of association cortex. The results provide an important addition to the literature on genetic mediation of attention (64) and, more generally, of cognition (65) by demonstrating that genetics can alter the course of cognitive aging (see also ref. 66 and http://www.nih.gov/nia/research/meetings/age-wg.htm). Additional work will be needed to determine whether the attentional changes in APOE ε4 carriers reported here extend back before the fifth decade of life.

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